REMARKS

Applicant has cancelled nonelected claims 5 and 15-21 as required under 37 CFR §1.144. For the sake of clarity, Applicant has cancelled pending Claims 1-4, 6-14 and 22-24 and added new Claims 28-41. These new claims add no new matter.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner has upheld the rejection of Claims 1, 3-4 and 6-14 under 35 U.S.C. §112, first paragraph, for not being enabling for the invention as claimed.

Applicants have cancelled Claims 1, 3-4 and 6-14 and replaced them with new claims 28-41.

Applicants have clearly demonstrated in the Specification, Examples 4-6, that the anti-proliferative effects of type I IFN are increased in human HT1080 cells transfected with a gene encoding the human IFNAR2c polypeptide when compared with the effects of type I IFN seen in untransfected HT1080 cells *in vitro* (see Example 1). Applicants have further demonstrated that this effect is also seen in an *in vivo* model, in which lung tumors derived from LOX human melanoma cells (parental or IFNAR2c-transfected) are treated with systemic Betaseron™ (see Example 6 and Figure 10).

Further evidence can be found in a recent publication by the inventors (Wagner et al. *Int. J. Cancer* (2004) 111:32-42. In this paper, an *in vivo* mouse xenograft model is used to examine the inhibition of cell proliferation of parental and IFNAR2c-transfected MDA231 cells, following treatment with a Type I IFN (see Specification, pg20, lines 18-25). The results (see Table III, pg 40), which use reduction in tumor burden as a measure of inhibition of cell proliferation, clearly indicate that transfection of human MDA231 cells with the IFNAR2c gene increases the sensitivity of these cells to treatment with a Type I IFN (Betaseron™).

The Specification describes treatment of diseases characterized by unwanted cell proliferation by increasing the number of cellular IFNAR2c receptors (pg 7, line 22 to pg 8, line 1). On page 7, lines 27-29 of the Specification, it states "The IFNAR2c gene may be delivered to the organism in any effective manner, e.g. using a vector or other delivery vehicle, or as naked DNA".

New claims 35, 37 and 40 describe different methods that are useful for the introduction of an exogenous gene, in this case, the human IFNAR2c gene, into human cells. The use of

electroporation with naked DNA or plasmid DNA is well-known by those of skill in the art. Viral vectors have been used for successful delivery of genes into cells, both *in vitro* and *in vivo*. For example, Qin et al. (*Proc. Natl. Acad. Sci.* 95:14411-14416, 1998) describes the use of viral vectors to deliver IFNβ to tumors *in vivo*, with resultant tumor regression. The present invention contemplates the use of gene therapy to deliver the gene encoding the IFNAR2c polypeptide to tumor cells responsive to type I IFNs to further increase the responsiveness of these cells to the IFNβ ligand.

Applicants believe that with the arguments presented above, presently pending claims 28-41 are enabled.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1, 3-4, 6-14 and 22-24 under 35 U.S.C. §112, second paragraph, for being indefinite. The Examiner has indicated that the phrase "the anti-growth effects" in claim 1 and its dependent claims is unclear as to which anti-growth effects are being claimed. The Examiner has also indicated that claims 22 and 24 are indefinite because the phrase "further comprising introducing exogenous polynucleotide encoding the IFNAR2c polypeptide into cells in culture to form said modified cell" does not make clear what the relationship or connection between cells in culture and a target cell population is.

Applicants have cancelled claims 1, 6-14 and 22-24 and replaced them with new claims 28-41. Applicants believe that pending claims 28-41 are not indefinite.

Rejection under 35 U.S.C. §102 (b)

The Examiner has maintained his rejection of Claims 1-4, 6 and 12-13 under 35 U.S.C. §102 (b) as being anticipated by Domanski et al. (*J. Biol. Chem.* 273:3144-3147, 1998).

The Domanski et al. reference describes experiments in which L-929 mouse cells have been transfected with and are co-expressing a wild-type human IFNα receptor chain and a series of mutant human IFNβ receptor chains. Domanski et al. show that these transfected cells demonstrate an anti-viral response in the presence of IFNβ. The Examiner argues that because these cells demonstrate the anti-viral effects of IFNβ, other effects seen in cells in response to treatment with type I IFNs are "inherent", and therefore the anti-growth effects claimed by the Applicant would be anticipated by this reference.

In another reference (Platanias et al., *J. Biol. Chem.* 273:5577-5581, 1998), this same group of investigators turned their attention to the antiproliferative response of transfected L-929 mouse cells to IFNβ (pg 7, line 22 to pg 8, line 1). The data demonstrates that while human IFNα2 and IFNβ produce an antiviral response in these cells (as described in the earlier Domanski et al. reference), the cells do not respond to the antiproliferative effects of human type I IFNs (see abstract).

Applicants have cancelled claims 1-4, 6 and 12-13 and replaced them with new claims 28-41, which refer specifically to human type I IFNs. Applicants believe that in light of the language of new claims 28-41, the rejection of the Examiner has been rendered mute.

Rejection under 35 U.S.C. §102 (b)

The Examiner has rejected Claims 1, 3-4, 6, 12-13 and 23 under 35 U.S.C. §102 (b) as being anticipated by Lutfalla et al. (*EMBO J.* 14:5100-5108, 1995).

Lutfalla et al. disclose experiments involving a mutant cell line, U5A, which is completely defective in IFN αβ binding. When these cells were stably transfected with a vector expressing human IFNAR2-2 (equivalent to IFNAR2c), the transfected U5A cells exhibited an anti-viral response when exposed to IFN αβ. The Examiner states that Lutfalla et al. anticipates the instant claims, arguing that an anti-growth response in these cells following exposure to IFN would be inherent.

Applicants have cancelled claims 1, 6-14 and 22-24 and replaced them with new claims 28-41. Lutfalla et al. does not describe a method of inhibiting cell proliferation in a human cell population which possesses functional IFNAR2c poplypeptide chains (see Claim 28).

By contrast, the experiments described in Lutfalla et al. all use a mutant human cell line, U5A, which is lacking functional IFN receptors. The authors state "These cells show neither binding nor response to IFN-αβ...U5A cells are defective in the cell surface expression of a receptor subunit recognized by an anti-IFN-αβ receptor monoclonal antibody" (see Lutfalla et al., pg 5103, first column). Experiments determined that the lack of responsiveness could not be corrected by transfection with the IFNAR2-1 subunit, but could only be restored by transfection with the IFNAR2 subunit.

Applicants believe that in light of new claims 28-41 and the arguments presented above, Lufalla et al. does not anticipate the instant claims and therefore respectfully request withdrawal of this rejection.

Conclusion:

Applicants believe that with the submission of newly drafted Claims 28-41 and the arguments presented above, the Claims are in condition for allowance.

Respectfully submitted,

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